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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,877	08/08/2002	Daniel Henry Densham	GJE-89	1425

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EXAMINER

WILDER, CYNTHIA B

ART UNIT	PAPER NUMBER
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1637

13

DATE MAILED: 03/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/089,877

Applicant(s)

DENSHAM, DANIEL HENRY

Examiner

Cynthia B. Wilder, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 5/23/2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22-45 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 22-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03 April 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 4/2/03, 5/23/03
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. Applicant's preliminary amendment filed on April 4, 2002 is acknowledged. Claims 1-21 have been canceled. Claims 22-45 have been added and are pending in the instant application.

Specification

2. The disclosure is objected to because of the following informalities:

(a) The disclosure is objected at pages 12 and 13 because the designation for the sequence identifier is improper (see MPEP§ 2422.03). It is suggested amending the disclosure at pages 12 and 13 to recite --SEQ ID NO:--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 22-35, 40, 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 22-35 are indefinite in claim 22 because the claims lack a final process step that clearly relates back to the preamble. The claims are drawn to a method of determining the sequence of a polynucleotide. However, the final step recites a step of "detecting conformational changes in an enzyme". Thus it cannot be determined if the goal of the preamble, i.e., for sequencing a polynucleotide is achieved or not and if achieved, in what step it is achieved. Likewise, it cannot be clearly determined if the claims are intended to recited "a method of sequencing a polynucleotide" or "a method of detecting a conformational change in an enzyme.

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While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion (see *ex parte Erlich*, 3 USPQ2d1011, p.1011 (Bd. Pat. Applicant. Int.1986). Clarification is required as to Applicant's intent.

(b) Claims 22, 40, 41 are indefinite at the recitation of "capable of " because it cannot be determined if the limitation after "capable of" is a property of the enzyme or a separate step. It is suggested amending the claims to recite positive, active language by changing "capable of interacting with and processing" to --that interacts with and process-- or some other language as supported by the specification as originally filed.

(c) Claim 28 is indefinite at the recitation of "capable of" because it cannot be determined if the limitation after "capable of" is a property of the label or a separate step. It is suggested amending the claim to recite positive, active language by changing " capable of" to --which interacts-- or some other language as supported by the specification as originally filed.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 22, 23 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Holzrichter et al (WO 95/06138, March 1995). Regarding claim 22, Holzrichter et al. teach a method of determining the sequence of a polynucleotide, comprising the step of: reacting a target polynucleotide with enzyme that is capable of interacting with and processing along the polynucleotide, under conditions sufficient to induce enzyme activity; and detecting

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conformational changes in the enzyme as the enzyme processes along the polynucleotide (see page 10-12, Section E, entitled "DNA sequencing"; see also example 1, first two paragraphs).

Regarding claim 23, Holzrichter et al teach the method of claim 22, wherein the enzyme is a polymerase (page 10, first two lines under Section E, entitled "DNAS sequencing").

Regarding claim 24, Holzrichter et al teach the method of claim 22, wherein the enzyme is immobilized on a solid support (bottom of page 10 bridging page 11, lines 1-2). Therefore, Holzrichter et al meet the limitations of claims 22, 23 and 25 of the instant invention.

Claim Rejections - 35 USC § 102(e)

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 22-27, 29, 31, 32, 34, 36-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Chan (US 6,210,896 B1, effective filing date August 13, 1998). Regarding claims 22 and 40, Chan teaches a method of determining the sequence of a polynucleotide, comprising the steps of (a) reacting a target polynucleotide with an enzyme that is capable of interacting with and processing along the polynucleotide, under conditions sufficient to induce enzyme activity; and detecting conformation changes in the enzyme process along the polynucleotide and wherein

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the enzyme contains a detectable label (col. 5, lines 29 to col. 8, lines 13, 53-64 and col. 9, lines 11-28).¹

Regarding claim 23, Chan teaches a method according to claim 22, wherein the enzyme is a polymerase (col. 7, lines 31-38).

Regarding claim 24, Chan teaches a method according to claim 22, wherein the enzyme is a helicase enzyme (col. 7, lines 31-33 and col. 8, lines 5-12).

Regarding claim 25, Chan teaches a method according to claim 22, wherein the enzyme is immobilized on a solid support (col. 9, lines 33-42).

Regarding claim 26, Chan teaches a method according to claim 25, comprising a plurality of enzymes immobilized on the solid support (col. 11, lines 57-61 and Figure 1).

Regarding claim 27, Chan teaches a method according to claim 22, wherein the enzyme comprises a first bound detectable label, the characteristics of which alter as the enzyme undergoes conformational change (col. 9, lines 11-36, col. 11, 24-56 and col. 12, lines 7-25; see also col. 24, line 54 to col. 25, line 58).

Regarding claim 29, Chan teaches a method according to claim 27, wherein a second detectable label is bound to a nucleotide brought in contact with the enzyme (col. 9, lines 11-36, col. 11, line 24 to col. 12, lines 25).

Regarding claim 31, Chan teaches the method according to claim 29, wherein the first label is an energy donor and the second label is an energy acceptor and wherein the second step is carried out by measuring energy transfer between the two labels (col. 9, lines 11-36, col. 11, line 24 to col. 12, lines 25).

¹ The conformational change as recited in the rejected claims additionally is an inherent property of the polymerase

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Regarding claims 32 and 34, Chan teaches the method according to claims 22 and 32, wherein the method is carried out using a confocal microscope and wherein said optical system detects single fluorophore polarization (see lines 40-67 and col. 36, line 56 to col. 37, lines 1-4).

Regarding claim 36, Chan teaches a method for determining the sequence of a polynucleotide, comprising detecting via fluorescence resonance energy transfer a conformation change in an enzyme that interacts with and process along a target polynucleotide, thereby permitting determining the sequence of the polynucleotide (col. 9, lines 11-36, col. 11, line 57 to col. 12, lines 1-6, col. 24, line 54 to col. 25, line 58 and col. 28, lines 1-18).

Regarding claim 37, Chan teaches the method according to claim 36, wherein the enzyme is a polymerase enzyme (col. 25, lines 28-29).

Regarding claim 38 and 39, Chan teaches a method according to claim 36, wherein the enzyme is immobilized on a solid support (col. 25, lines 7 and 8).

Regarding claim 41, Chan teaches a solid support comprising at least one immobilized enzyme capable of interacting with and processing along a target polynucleotide, the enzyme being labeled with one or more detectable labels (col. 9, lines 35-36, col. 11, lines 57-58 and figure 1; see also col. 29, lines 54-57).

Regarding claim 42, Chan teaches the solid support of claim 41, wherein the enzyme is a polymerase (col. 11, lines 57-58 and figure 1).

Regarding claims 43 and 44, Chan teaches the solid support of claims 41 and 42, wherein the label is a fluorophore (col. 11, lines 57-61).

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Regarding claim 45, Chan teaches a system for determining a sequence of a polynucleotide, comprising a solid support according to claim 41, and an apparatus for detecting the label (col. 9, line 29-45 and example 6).

Therefore, Chan meets the limitation of claims 22-27, 29, 31, 32, 34, 36-45 of the instant invention.

9. Claim 33 is rejected under 35 U.S.C. 102(e) as being anticipated by Chan (US 6,355,420 B1, filing date August 1998). Regarding claim 33, Chan teaches a method of determining the sequence of a polynucleotide, comprising the steps of (a) reacting a target polynucleotide with an enzyme that is capable of interacting with and processing along the polynucleotide, under conditions sufficient to induce enzyme activity; and detecting conformation changes in the enzyme process along the polynucleotide and wherein the enzyme contains a detectable label and wherein the detecting is carried out by fluorescence imaging (col. 35, line 16 to col. 36, line 21). Therefore, Chan meets the limitations of claim 33 of the instant invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claim 28, 30, 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chan ('896) as previously applied above in view of Ha et al (Proc. Natl. Acad. Sci. USA, February

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1999). Regarding claim 28, 30 and 35, Chan teaches a method of determining the sequence of a polynucleotide, comprising the steps of (a) reacting a target polynucleotide with an enzyme that is capable of interacting with and processing along the polynucleotide, under conditions sufficient to induce enzyme activity; and detecting conformation changes in the enzyme process along the polynucleotide and wherein the enzyme contains a detectable label. Chan further teaches wherein the second step is carried out using confocal microscopy. The reference of Chan et al. differs from the instant invention in that Chan do not expressly teach wherein that the enzyme is bound with a first and second detectable label nor does the reference expressly teach wherein the detection step is carried out by fluorescence polarization anisotropy (FPA). However, FPA is well-known and commonly used in the art to assess the effects of a ligand binding on a target nucleic acid's stability and/or conformation. For example in a general teaching, Ha et al teach the use of fluorescence polarization anisotropy to observe conformational fluctuations and catalytic reactions of an enzyme (e.g., *staphylococcal* nuclease (SNase)) at single molecule resolution (page 893, col. 1, last five lines of second paragraph). Ha et al teach that to probe the conformational dynamics of SNase and its interactions with substrate at single molecule resolution, three separate experiments were performed, one of which comprised doubly labeling the SNase enzyme with a donor and acceptor fluorophore and measuring fluorescence polarization anisotropy (abstract and Figure 3 & legend). Ha et al disclose that that the method revealed distinct patterns of fluctuations that may be attributed to protein conformational dynamics on the millisecond time scale (abstract). Likewise, the reference teaches that the method is useful in studies of protein folding and enzyme catalysis at single molecule resolution (Abstract). Therefore, in view of the teachings of Ha et al, one of

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ordinary skill in the art would have been motivated at the time of the claimed invention to have been motivated to have modified the method of determining a sequence as taught by Chan to encompass detecting conformation changes of the enzyme by fluorescence polarization anisotropy. One of ordinary skill in the art would have been motivated to do so for the benefits taught by Ha et al. that fluorescence polarization anisotropy is useful in studies of protein folding and enzyme catalysis at single molecule resolution.

Prior Art

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Laing et al US 6, 332, 392 B1, December 18, 2001) teach a method of screening for bioactive compounds with affinity for nucleic acids using fluorescence polarization anisotropy.

Conclusion

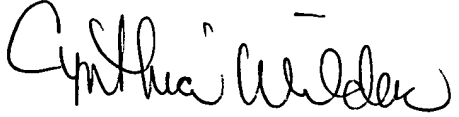
12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


CYNTHIA WILDER
PATENT EXAMINER